

## WO9854093

Publication Title:

NOVEL ANGIOGENESIS INHIBITORS

Abstract:

The present invention relates to compounds which inhibit tyrosine kinase enzymes, compositions which contain tyrosine kinase inhibiting compounds and methods of using tyrosine kinase inhibitors to treat tyrosine kinase-dependent diseases/conditions such as angiogenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases, in mammals.

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>6</sup> :</b> <b>C01D 239/72, 401/00, A01N 43/54</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/54093</b> <b>(43) International Publication Date:</b> 3 December 1998 (03.12.98)
<b>(21) International Application Number:</b> PCT/US98/10590 <b>(22) International Filing Date:</b> 26 May 1998 (26.05.98) <b>(30) Priority Data:</b> 60/048,076                      30 May 1997 (30.05.97)                      US 9800681.0                      14 January 1998 (14.01.98)                      GB <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BILODEAU, Mark, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HUNGATE, Randall, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KENDALL, Richard, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). RUTLEDGE, Ruth [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). THOMAS, Kenneth, A., Jr. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). RUBINO, Robert [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FRALEY, Mark, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(74) Common Representative:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> NOVEL ANGIOGENESIS INHIBITORS <b>(57) Abstract</b> <p>The present invention relates to compounds which inhibit tyrosine kinase enzymes, compositions which contain tyrosine kinase inhibiting compounds and methods of using tyrosine kinase inhibitors to treat tyrosine kinase-dependent diseases/conditions such as angiogenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases, in mammals.</p>		

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TITLE OF THE INVENTION

## NOVEL ANGIOGENESIS INHIBITORS

BACKGROUND OF THE INVENTION

5           The present invention relates to compounds which inhibit tyrosine kinase enzymes, compositions which contain tyrosine kinase inhibiting compounds and methods of using tyrosine kinase inhibitors to treat tyrosine kinase-dependent diseases/conditions such as neoangiogenesis, cancer,  
10   atherosclerosis, diabetic retinopathy or inflammatory diseases, in mammals.

          Tyrosine kinases are a class of enzymes that catalyze the transfer of the terminal phosphate of adenosine triphosphate to tyrosine residues in protein substrates. Tyrosine kinases are  
15   believed, by way of substrate phosphorylation, to play critical roles in signal transduction for a number of cell functions. Though the exact mechanisms of signal transduction is still unclear, tyrosine kinases have been shown to be important contributing factors in cell proliferation, carcinogenesis and cell differentiation.  
20   Accordingly, inhibitors of these tyrosine kinases are useful for the prevention and treatment chemotherapy of proliferative diseases dependent on these enzymes.

          For example, a method of treatment described herein relates to neoangiogenesis. Neoangiogenesis occurs in conjunction  
25   with tumor growth and in certain diseases of the eye. It is characterized by excessive activity of vascular endothelial growth factor.

          Vascular endothelial growth factor (VEGF) binds the high affinity membrane-spanning tyrosine kinase receptors KDR  
30   and Flt-1. Cell culture and gene knockout experiments indicate that each receptor contributes to different aspects of angiogenesis. KDR mediates the mitogenic function of VEGF whereas Flt-1 appears to modulate non-mitogenic functions such as those

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associated with cellular adhesion. Inhibiting KDR thus modulates the level of mitogenic VEGF activity.

Vascular growth in the retina leads to visual degeneration culminating in blindness. VEGF accounts for most of the angiogenic activity produced in or near the retina in diabetic retinopathy. Ocular VEGF mRNA and protein are elevated by conditions such as retinal vein occlusion in primates and decreased pO<sub>2</sub> levels in mice that lead to neovascularization. Intraocular injections of anti-VEGF monoclonal antibodies or VEGF receptor immunofusions inhibit ocular neovascularization in both primate and rodent models. Regardless of the cause of induction of VEGF in human diabetic retinopathy, inhibition of ocular VEGF is useful in treating the disease.

Expression of VEGF is also significantly increased in hypoxic regions of animal and human tumors adjacent to areas of necrosis. Monoclonal anti-VEGF antibodies inhibit the growth of human tumors in nude mice. Although these same tumor cells continue to express VEGF in culture, the antibodies do not diminish their mitotic rate. Thus tumor-derived VEGF does not function as an autocrine mitogenic factor. Therefore, VEGF contributes to tumor growth in vivo by promoting angiogenesis through its paracrine vascular endothelial cell chemotactic and mitogenic activities. These monoclonal antibodies also inhibit the growth of typically less well vascularized human colon cancers in athymic mice and decrease the number of tumors arising from inoculated cells. Viral expression of a VEGF-binding construct of Flk-1, the mouse KDR receptor homologue, truncated to eliminate the cytoplasmic tyrosine kinase domains but retaining a membrane anchor, virtually abolishes the growth of a transplantable glioblastoma in mice presumably by the dominant negative mechanism of heterodimer formation with membrane spanning endothelial cell VEGF receptors. Embryonic stem cells, which normally grow as solid tumors in nude mice, do not produce detectable tumors if both VEGF alleles are knocked out. Taken

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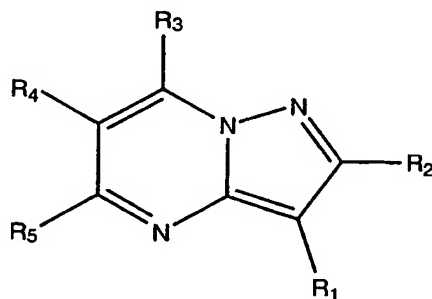
together, these data indicate the role of VEGF in the growth of solid tumors. Inhibition of KDR or Flt-1 is implicated in pathological neoangiogenesis, and these are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer.

Cancers which are treatable in accordance with the present invention demonstrate high levels of gene and protein expression. Examples of such cancers include cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung. These include histiocytic lymphoma, lung adenocarcinoma and small cell lung cancers. Additional examples include cancers in which overexpression or activation of Raf-activating oncogenes (e.g., K-ras, erb-B) is observed. More particularly, such cancers include pancreatic and breast carcinoma.

#### SUMMARY OF THE INVENTION

A compound is disclosed in accordance with formula

I:



I

or a pharmaceutically acceptable salt, hydrate or prodrug thereof,

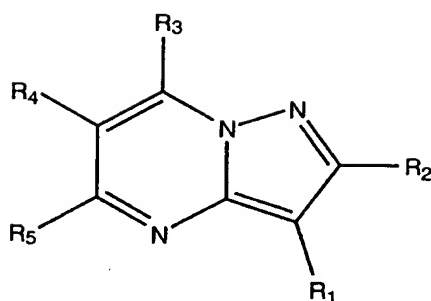
wherein

R<sub>1</sub> is H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>5-10</sub> aryl, halo, OH, C<sub>3-</sub>  
heterocyclyl, or C<sub>5-10</sub> heteroaryl; said alkyl, alkenyl,  
alkynyl, aryl, heteroaryl and heterocyclyl being

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- optionally substituted with from one to three members selected from R<sup>a</sup>;
- 5 R<sub>2</sub>&R<sub>3</sub> are independently H, C<sub>1-6</sub> alkyl, C<sub>5-10</sub> aryl, C<sub>3-6</sub> cycloalkyl, OH, NO<sub>2</sub>, -NH<sub>2</sub>, or halogen;
- R<sub>4</sub> is H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, C<sub>1-6</sub> alkoxyNR<sub>7</sub>R<sub>8</sub>, NO<sub>2</sub>, OH, -NH<sub>2</sub> or C<sub>5-10</sub> heteroaryl, said  
10 alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>;
- 15 R<sub>5</sub> is H, or C<sub>1-6</sub> alkyl, OR, halo, NH<sub>2</sub> or NO<sub>2</sub>;
- R<sup>a</sup> is H, C<sub>1-10</sub> alkyl, halogen, NO<sub>2</sub>, OR, -NR, NR<sub>7</sub>R<sub>8</sub>, R<sub>7</sub>R<sub>8</sub>, C<sub>5-10</sub> aryl, C<sub>5-10</sub> heteroaryl or C<sub>3-10</sub> heterocyclyl,
- 20 R is H, or C<sub>1-6</sub> alkyl; and
- R<sub>7</sub>&R<sub>8</sub> are independently H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, COR, COOR, COO-, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, or C<sub>5-10</sub> heteroaryl or NR<sub>7</sub>R<sub>8</sub> can be taken together to form a  
25 heterocyclic 5-10 membered saturated or unsaturated ring containing, in addition to the nitrogen atom, one  
to two additional heteroatoms selected from the group consisting of N, O and S.
- 30 Also disclosed is a pharmaceutical composition which is comprised of a compound represented by the formula I:

- 5 -



I

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are described as above or a pharmaceutically acceptable salt or hydrate or prodrug thereof in combination with a carrier.

Also included is a method of treating a tyrosine kinase dependent disease or condition in a mammal which comprises administering to a mammalian patient in need of such treatment a tyrosine kinase dependent disease or condition treating amount of a compound of formula I or a pharmaceutically acceptable salt, hydrate or pro-drug thereof.

Also included is a method of treating cancer in a mammalian patient in need of such treatment which is comprised of administering to said patient an anti-cancer effective amount of a compound of formula I or a pharmaceutically acceptable salt, hydrate or pro-drug thereof.

Also included in the present invention is a method of treating diseases in which neoangiogenesis is implicated, which is comprised of administering to a mammalian patient in need of such treatment a compound of formula I or a pharmaceutically acceptable salt, hydrate or pro-drug thereof in an amount which is effective for reducing neoangiogenesis.

More particularly, a method of treating ocular disease in which neoangiogenesis occurs is included herein, which is comprised of administering to a mammalian patient in need of such treatment a compound of formula I or a pharmaceutically acceptable salt hydrate or pro-drug thereof in an amount which is effective for treating said ocular disease.



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More particularly, a method of treating retinal vascularization is included herein, which is comprised of administering to a mammalian patient in need of such treatment a compound of formula I or a pharmaceutically acceptable salt, hydrate or pro-drug thereof in an amount which is effective for treating retinal vascularization. Diabetic retinopathy is an example of a disease in which neoangiogenesis or retinal vascularization is part of the overall disease etiology. Also included is a method of treating age-related macular degeneration.

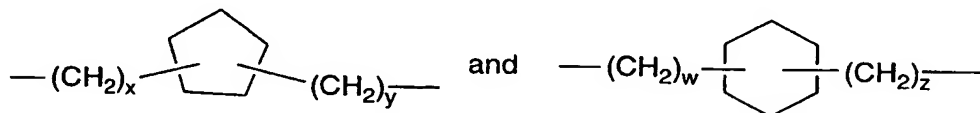
These and other aspects of the invention will be apparent from the teachings contained herein.

#### DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopropyl, cyclobutyl, cycloheptyl, cyclopentyl and cyclohexyl.

Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion. Examples include the following:



wherein:  $x + y = \text{from } 0\text{--}10$ ; and  $w + z = \text{from } 0\text{--}9$ .

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

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When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups of  $R^a$ , described herein.

The term "alkenyl" refers to a hydrocarbon radical  
5 straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred alkenyl groups include ethenyl, propenyl,  
10 butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted with one to three groups of  $R^a$ , when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical  
15 straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the  
20 alkynyl group may contain triple bonds and may be substituted with 1-3 groups of  $R^a$ , when a substituted alkynyl group is provided.

Aryl refers to 5-10 membered aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least  
25 one ring having at least 5 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted with 1-3 groups of  $R^a$  as defined herein.  
30 Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups.

The term heterocycle, heteroaryl or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic

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heterocyclic ring system, any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The heterocycle, heteroaryl or heterocyclic may be substituted with 1-3 groups of R<sup>a</sup>. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thiophenyl, imidazopyridinyl, tetrazolyl, triazinyl, thienyl, benzothienyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. The term "alkoxy" refers to those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy, allyloxy, propargyloxy, and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

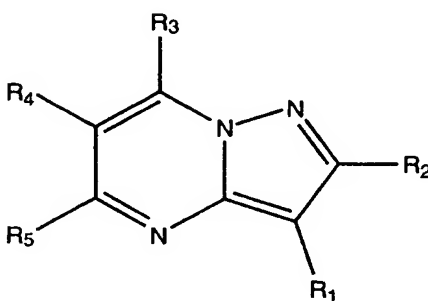
The term "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the drug in vivo via some metabolic process. Exemplary prodrugs include acyl amides of the amino compounds of this

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invention such as amides of alkanolic(C<sub>1-6</sub>)acids, amides of aryl acids (e.g., benzoic acid) and alkane(C<sub>1-6</sub>)dioic acids.

Tyrosine kinase dependent diseases or conditions refers to hyperproliferative disorders which are initiated/maintained by aberrant tyrosine kinase enzyme activity. Examples include psoriasis, cancer, immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, angiogenesis (e.g. tumor growth, diabetic retinopathy), etc.

The compounds of the present invention are in accordance with formula I:



I

or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein

R<sub>1</sub> is H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>5-10</sub> aryl, halo, OH, C<sub>3-10</sub> heterocyclyl, or C<sub>5-10</sub> heteroaryl; said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>;

R<sub>2</sub>&R<sub>3</sub> are independently H, C<sub>1-6</sub> alkyl, C<sub>5-10</sub> aryl, C<sub>3-6</sub> cycloalkyl, OH, NO<sub>2</sub>, -NH<sub>2</sub>, or halogen;

R<sub>4</sub> is H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, C<sub>1-6</sub>

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alkoxyNR<sub>7</sub>R<sub>8</sub>, NO<sub>2</sub>, OH, -NH<sub>2</sub> or C<sub>5-10</sub> heteroaryl, said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>;

5

R<sub>5</sub> is H, or C<sub>1-6</sub> alkyl, OR, halo, NH<sub>2</sub> or NO<sub>2</sub>;

R<sup>a</sup> is H, C<sub>1-10</sub> alkyl, halogen, NO<sub>2</sub>, OR, -NR, NR<sub>7</sub>R<sub>8</sub>, R<sub>7</sub>R<sub>8</sub>, C<sub>5-10</sub> aryl, C<sub>5-10</sub> heteroaryl or C<sub>3-10</sub> heterocyclyl,

10

R is H, or C<sub>1-6</sub> alkyl; and

15

R<sub>7</sub>&R<sub>8</sub> are independently H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, COR, COOR, COO-, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, or C<sub>5-10</sub> heteroaryl or NR<sub>7</sub>R<sub>8</sub> can be taken together to form a heterocyclic 5-10 membered saturated or unsaturated ring containing, in addition to the nitrogen atom, one to two additional heteroatoms selected from the group consisting of N, O and S.

20

A preferred subset of compounds of the present invention is realized when:

25

R<sub>1</sub> is H, C<sub>1-10</sub> alkyl, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, or C<sub>5-10</sub> heteroaryl; said alkyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>;

30

R<sub>2</sub>&R<sub>3</sub> are independently H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, OH, or halogen;

R<sub>4</sub> is H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>5-10</sub> aryl, C<sub>5-10</sub> heteroaryl, C<sub>3-10</sub> heterocyclyl, C<sub>1-6</sub> alkoxyNR<sub>7</sub>R<sub>8</sub>, NO<sub>2</sub>, OH, -NH<sub>2</sub> or C<sub>5-10</sub> heteroaryl, said alkyl, aryl,

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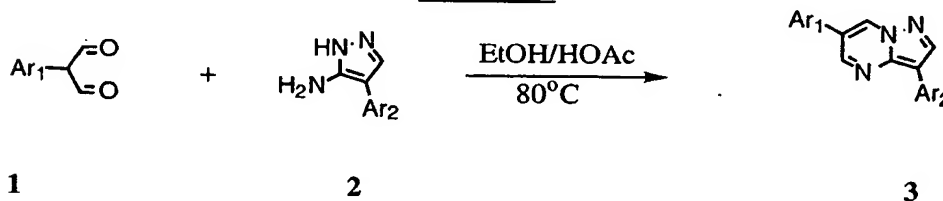
heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>; and all other variables are as described above.

- 5                   Examples of the compounds of this invention are:
- 3-(4-fluorophenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-chlorophenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(3,4-methylenedioxyphenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
10 3-(phenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-fluorophenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-chlorophenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-thienyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-acetamidophenyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
15 3-(3-thienyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-acetamidophenyl)-6-(4-methoxyphenyl)pyrazolo(1,5-A)pyrimidine,  
20 3-(3-thienyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-chlorophenyl) pyrazolo(1,5-A)pyrimidine.  
3-(4-pyridyl)-6-(4-chlorophenyl) pyrazolo(1,5-A)pyrimidine,  
25 3-(phenyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(2-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(2-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
30 3-(4-pyridyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(2-pyrazinyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(2-pyrazinyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,

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- 3-(3-pyridyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
 3-(4 pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
 3-(3-thienyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
 3-(3-thienyl)-6-(4-hydroxyphenyl)pyrazolo(1,5-A)pyrimidine,  
 5 3-(3-thienyl)-6-(4-(2-(4-morpholinyl)ethoxy)phenyl) pyrazolo(1,5-A)pyrimidine,  
 3-(3-thienyl)-6-(cyclohexyl)pyrazolo (1,5-A)pyrimidine,  
 3-(bromo)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
 3-(bromo)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
 10 3-(phenyl)-6-(2-(3-carboxy)pyridyl) pyrazolo(1,5-A)pyrimidine,  
 and  
 3-(3-thienyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine.

Schemes 1-3 for preparing the novel compounds of  
 15 this invention are presented below. The examples which follow the  
 schemes illustrate the compounds that can be synthesized by  
 Schemes 1-3, but Schemes 1-3 are not limited by the compounds  
 in the tables nor by any particular substituents employed in the  
 schemes for illustrative purposes. The examples specifically  
 20 illustrate the application of the following schemes to specific  
 compounds.

Scheme 1

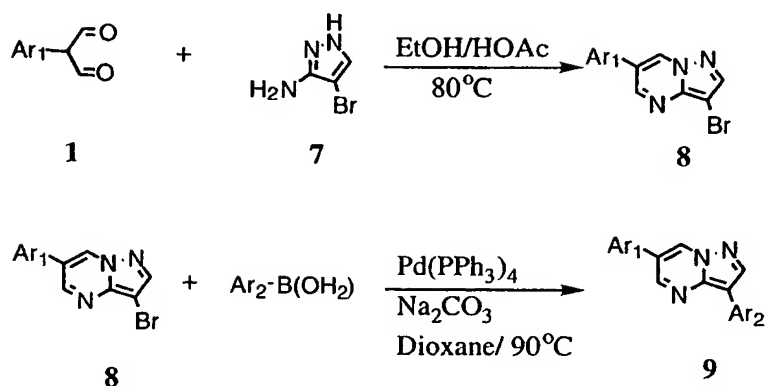
25

Generally, a method for the preparation of 3,6-diaryl  
 pyrazolo(1,5-A)pyrimidines comprises mixing a commercially  
 available malondialdehyde compound (1), with commercially  
 available aminopyrazole (2) in an alcohol, such as ethanol,  
 30 methanol, isopropanol, butanol and the like, said alcohol containing  
 catalytic quantities of an acid, such as acetic acid, to yield (3),

- 13 -

wherein Ar1 and Ar2, respectively, are R4 and R1, as described above.

### Scheme 2



5

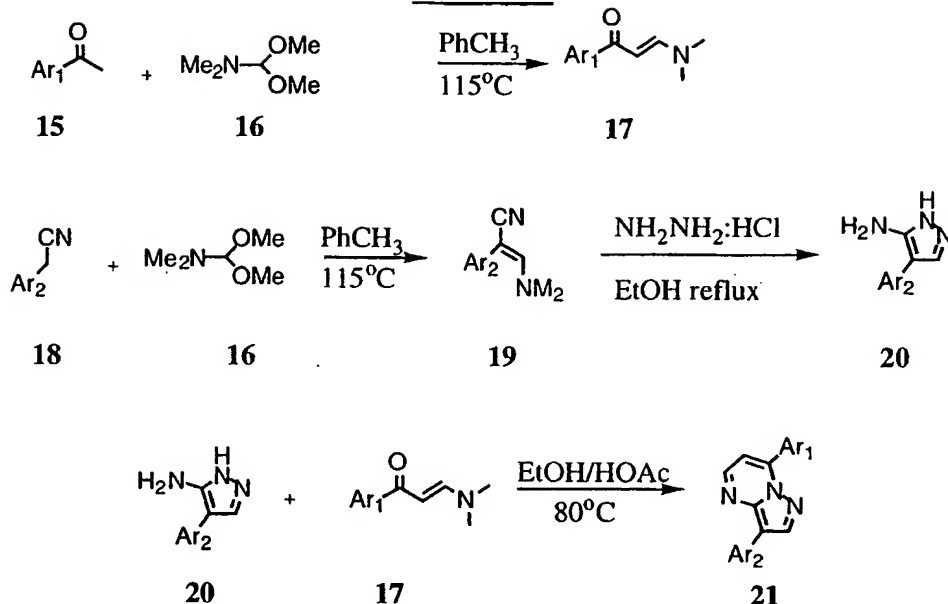
Scheme 2 depicts a means for making 3,6-diaryl pyrazolo(1,5-A)pyrimidines when the desired aminopyrazole is not commercially available. In a like manner to that described in  
 10 scheme 1 compound (8) is obtained. Treatment of (8) with a boronic acid derivative in the presence of a palladium catalyst provides after workup the desired material (9). Ar1 and Ar2 are as described above.

15



- 14 -

Scheme 3



Scheme 3 illustrates another method for the preparation of 3,7 diarylpyrazolo(1,5-A)pyrimidines. The commercially available ketone (15) and nitrile (18) are treated separately with dimethylformamidedimethyl acetal (16) in refluxing toluene to give products (17) and (19) respectively. Compound (19) is then treated with hydrazinehydrochloride in refluxing ethanol to give the aminopyrazole (20). Compounds (17) and (20) and then treated with catalytic amounts of acetic acid in ethanol as described previously giving the desired of 3,7 diarylpyrazolo(1,5-A)pyrimidines (21). Ar<sub>1</sub> and Ar<sub>2</sub> are as described above.

The invention described herein includes a pharmaceutical composition which is comprised of a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof in combination with a carrier. As used herein the terms "pharmaceutically acceptable salts" and "hydrates" refer to those salts and hydrated forms of the compound which would be apparent to the pharmaceutical chemist, i.e., those which favorably affect the physical or pharmacokinetic properties of the compound, such as solubility, palatability, absorption, distribution, metabolism

- 15 -

and excretion. Other factors, more practical in nature, which are also important in the selection, are the cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug.

5                   When a compound of formula I is present as a salt or hydrate which is non-pharmaceutically acceptable, this can be converted to a salt or hydrate form which is pharmaceutically acceptable in accordance with the present invention.

                  When the compound is negatively charged, it is  
10   balanced by a counterion, e.g., an alkali metal cation such as sodium or potassium. Other suitable counterions include calcium, magnesium, zinc, ammonium, or alkylammonium cations such as tetramethylammonium, tetrabutylammonium, choline, triethylhydroammonium, meglumine, triethanolhydroammonium,  
15   etc. An appropriate number of counterions is associated with the molecule to maintain overall charge neutrality. Likewise when the compound is positively charged, e.g., protonated, an appropriate number of negatively charged counterions is present to maintain overall charge neutrality.

20                   Pharmaceutically acceptable salts also include acid addition salts. Thus, the compound can be used in the form of salts derived from inorganic or organic acids or bases. Examples include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate,  
25   camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate,  
30   persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and

- 16 -

magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as  
5 lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.  
10 Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms  
15 being included in the present invention. When any variable (e.g., aryl, heterocycle, R<sub>1</sub>, etc) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise stated.

20 The compounds of the invention can be formulated in a pharmaceutical composition by combining the compound with a pharmaceutically acceptable carrier. Examples of such compositions and carriers are set forth below.

The compounds may be employed in powder or  
25 crystalline form, in solution or in suspension. They may be administered orally, parenterally (intravenously or intramuscularly), topically, transdermally or by inhalation.

Thus, the carrier employed may be, for example, either a solid or liquid. Examples of solid carriers include lactose,  
30 terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Examples of liquid carriers include syrup, peanut oil, olive oil, water and the like. Similarly, the carrier for oral use may include time delay material well known in

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the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders. Such topical formulations can be used to treat ocular diseases as well as inflammatory diseases such as rheumatoid arthritis, psoriasis, contact dermatitis, delayed hypersensitivity reactions and the like.

Examples of oral solid dosage forms include tablets, capsules, troches, lozenges and the like. The size of the dosage form will vary widely, but preferably will be from about 25 mg to about 500mg. Examples of oral liquid dosage forms include solutions, suspensions, syrups, emulsions, soft gelatin capsules and the like. Examples of injectable dosage forms include sterile injectable liquids, e.g., solutions, emulsions and suspensions. Examples of injectable solids would include powders which are reconstituted, dissolved or suspended in a liquid prior to injection.

In injectable compositions, the carrier is typically comprised of sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

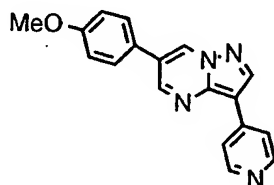
For the methods of treatment disclosed herein, dosages can be varied depending upon the overall condition of the patient, the nature of the illness being treated and other factors. An example of a suitable oral dosage range is from about 0.1 to about 80 mg/kg per day, in single or divided doses. An example of a suitable parenteral dosage range is from about 0.1 to about 80 mg/kg per day, in single or divided dosages, administered by intravenous or intramuscular injection. An example of a topical dosage range is from about 0.1 mg to about 150 mg, applied externally from about one to four times a day. An example of an inhalation dosage range is from about 0.01 mg/kg to about 1 mg/kg per day.

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The compounds may be administered in conventional dosages as a single agent or in combination with other therapeutically active compounds.

### EXAMPLE 1

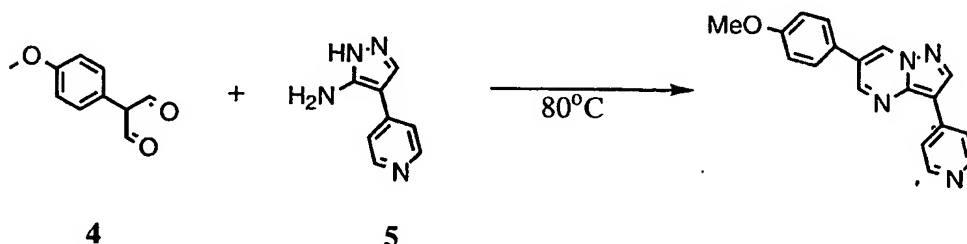
5



3-(4 pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine

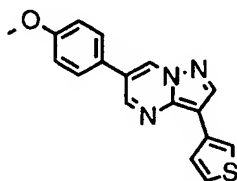
A solution of commercially available dialdehyde (4, 12.9 mg, 0.0724 mmol) and aminopyrazole (5, 10.4mg 0.0652mmol) in ethanol was heated at 80°C for 10 hours in a test tube containing catalytic amounts of acetic acid. The reaction was cooled to room temperature and the yellow solid was collected by filtration and the title compound was washed with cold ethanol and dried (11.7 mg, 60%). Mass Spec (M+1, 303).

15



20

### EXAMPLE 2

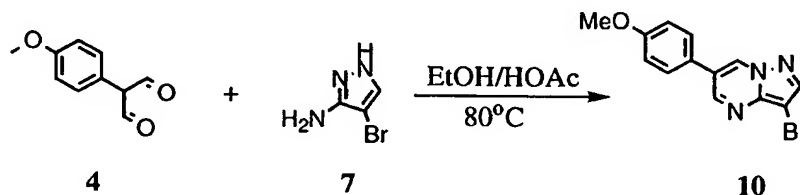


3-(3-thienyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine

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## Step 1.

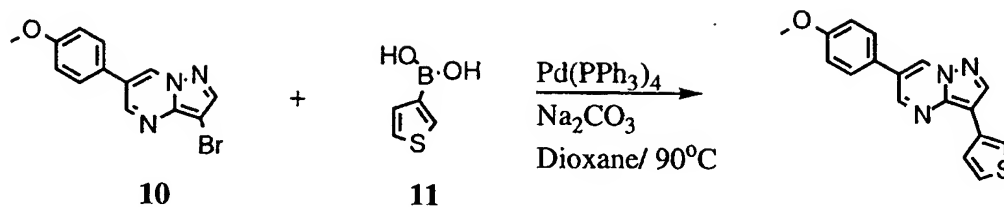
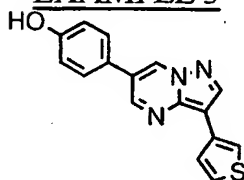
A solution of **4** (713 mg, 4.0 mmol) and commercially available **7** (648 mg, 4.0 mmol), discussed above in ethanol (20 mL) was heated at 75°C for 4 h. The resulting white suspension was as described in example 1 for 4 hours, then cooled to 20°C, filtered, and washed with methanol (3 x 5 mL) to provide **10** as a white powder (1.07 g, 88%, mp = 168-170°C): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.79 (d, 1 H, *J* = 2.2 Hz), 8.74 (d, 1 H, *J* = 2.2 Hz), 8.12 (s, 1 H), 7.51 (d, 2 H, *J* = 8.8 Hz), 7.05 (d, 2 H, *J* = 8.8 Hz), 3.88 (s, 3 H).



## Step 2.

A suspension of (**10**) (250 mg, 0.82 mmol), thiophene-3-boronic acid (**11**) (158 mg, 1.24 mmol), and aqueous sodium carbonate (2 M, 1 mL) in dioxane (5 mL) was de-gassed by evacuating and backflushing with argon (3x). Tetrakis(triphenyl-phosphine) palladium (20 mg, 0.017 mmol) was added and the reaction mixture was de-gassed again. The argon filled flask was then submerged in an oil bath pre-heated to 90°C and was heated at that temperature for 16 h. After cooling to 20°C, the yellow precipitate which formed was collected by filtration and was washed with methanol (3 x 5 mL) to provide the title compound as a yellow powder (220 mg, 87%, mp = 191-193 °C): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.79 (d, 1 H, *J* = 2.4 Hz), 8.76 (d, 1 H, *J* = 2.2 Hz), 8.37 (s, 1 H), 7.90 (dd, 1 H, *J* = 2.9, 1.3 Hz), 7.70 (dd, 1 H, *J* = 4.9, 1.2 Hz), 7.54 (d, 2 H, *J* = 8.8 Hz), 7.43 (d, 1 H, *J* = 4.9, 2.9 Hz), 7.06 (d, 2 H, *J* = 8.8 Hz), 3.88 (s, 3H).

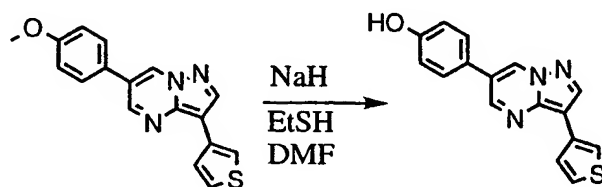
- 20 -

EXAMPLE 3

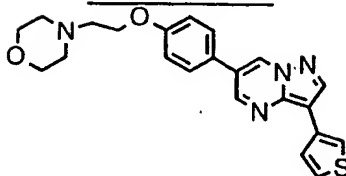
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## 3-(3-thienyl)-6-(4-hydroxyphenyl)pyrazolo(1,5-A)pyrimidine

Ethanethiol (30 mg, 36  $\mu\text{L}$ ) was added dropwise over 1 min to a suspension of sodium hydride (23 mg, 0.98 mmol) in dry DMF (2 mL) under argon. After 15 min, the compound of example 2 (50 mg, 0.16 mmol) was added and the reaction mixture was heated at 150°C for 1.5 h. The resulting brown solution was cooled, poured into water (25 mL) and washed with ethyl acetate (2 x 25 mL). The combined organics were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated, and purified by flash chromatography (40% EtOAc/Hexanes) to give the title compound as a yellow solid [11 mg, 23%,  $R_f$  = 0.12 (40% EtOAc/Hexanes)]:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.96 (d, 1 H,  $J$  = 2.4 Hz), 8.85 (d, 1 H,  $J$  = 2.2 Hz), 8.44 (s, 1 H), 7.94 (dd, 1 H,  $J$  = 2.9, 1.2 Hz), 7.74 (dd, 1 H,  $J$  = 4.9, 1.2 Hz), 7.56 (d, 2 H,  $J$  = 8.8 Hz), 7.46 (dd, 1 H,  $J$  = 4.9, 2.9 Hz), 6.94 (d, 2 H,  $J$  = 8.6 Hz).

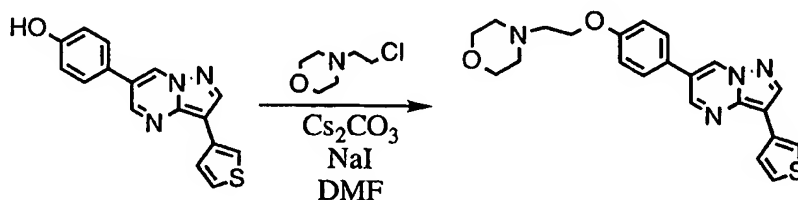


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EXAMPLE 4

3-(3-thienyl)-6-(4-(2-(4-morpholinyl)ethoxy)phenyl) pyrazolo(1,5-  
 5 A)pyrimidine

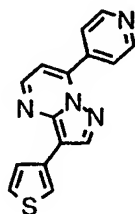
A solution of example 3 (11 mg, 0.038 mmol), cesium carbonate (37 mg, 0.11 mmol), N-(2-chloroethyl)morpholine hydrochloride (7 mg, 0.11 mmol), and sodium iodide (0.013 mmol)  
 10 in DMF (3 mL) was heated at 60°C under argon for 16 h. The reaction mixture was then poured into water (25 mL) and washed with ethyl acetate (2 x 25 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by flash chromatography [50% Hexanes/CHCl<sub>3</sub>(NH<sub>3</sub>)] to give the title compound as a yellow  
 15 solid [10 mg, 65%, mp = 149-151°C, *R<sub>f</sub>* = 0.39 (100% CHCl<sub>3</sub>(NH<sub>3</sub>))]: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.77 (d, 1 H, *J* = 2.2 Hz), 8.75 (d, 1 H, *J* = 2.2 Hz), 8.36 (s, 1 H), 7.90 (dd, 1 H, *J* = 2.9, 1.3 Hz), 7.69 (dd, 1 H, *J* = 4.9, 1.3 Hz), 7.52 (d, 2 H, *J* = 8.8 Hz), 7.43 (d, 1 H, *J* = 4.9, 2.9 Hz), 7.06 (d, 2 H, *J* = 8.8 Hz), 4.18  
 20 (t, 2 H, *J* = 5.7 Hz), 3.76 (t, 4 H, *J* = 4.6 Hz), 2.85 (t, 2 H, *J* = 5.7 Hz), 2.61 (t, 4 H, *J* = 4.6 Hz); FAB MS (*M*<sup>+</sup>+1) Anal Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>4</sub>O<sub>2</sub>S : C, 65.00; H, 5.46; N, 13.78. Found C, 64.98; H, 5.55; N, 14.02.



25



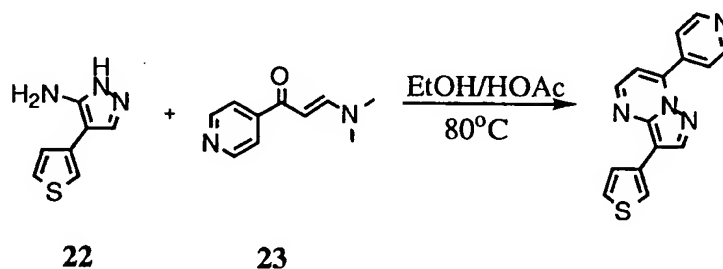
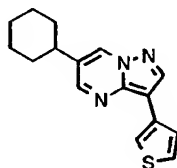
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EXAMPLE 5

5 3-(3-thiophenyl)-7-(4-pyridyl) pyrazolo(1,5-A)pyrimidine

A 13 x 100 mm reaction tube was charged with aminopyrazole (**22**) (16.5 mg, 0.100 mmol) dissolved in 0.500 mL EtOH and vinylogous amide (**23**) (17.6 mg, 0.100 mmol) dissolved in 0.200 mL EtOH. Glacial acetic acid (1 drop) was added and the reaction was heated to 80 °C for 14 h. An additional 0.100 mL of glacial acetic acid was added and heating was continued for an additional 6 h. The sample was concentrated to dryness to provide the desired title compound. Analysis by mass spectrometry

15 showed  $[M+H]^+$  279.2.

EXAMPLE 6

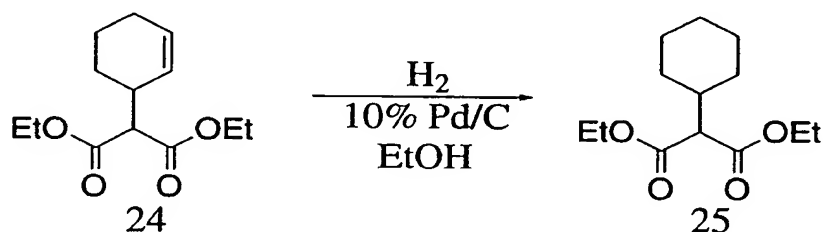
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3-(3-thienyl)-6-(cyclohexyl) pyrazolo(1,5-A)pyrimidine

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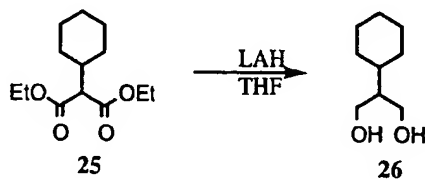
## Step 1

Palladium on carbon (10%, 2 g) was added to a solution of **24** (5.62 g, 23.4 mmol) in ethanol (100 mL) under an argon atmosphere. After evacuating and backflushing the reaction vessel with H<sub>2</sub> (3X), the black suspension was stirred vigorously under an H<sub>2</sub> filled balloon for 16 h. The reaction mixture was then filtered through celite, washed with ethyl acetate (200 mL) and concentrated to provide **25** as a colorless oil (5.0 g, 88%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.18 (q, 4 H, *J* = 7.1 Hz), 3.13 (d, 1 H, *J* = 9.2 Hz), 2.08 (m, 1 H), 1.73 - 1.56 (m, 5 H), 1.35 - 1.01 (m, 5 H), 1.26 (t, 6 H, *J* = 7.0 Hz).



## Step 2

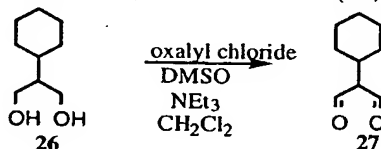
A solution of **25** (2.0 g, 8.3 mmol) in dry THF (30 mL) at 0°C was treated with lithium aluminum hydride (1.0 M in THF, 16.5 mL, 16.5 mmol) over a 5 min period. The reaction mixture was warmed gradually to 15°C over 20 min and then was re-cooled to 0°C and quenched sequentially with water (630 uL), aqueous sodium hydroxide (1 N, 630 uL), and then water (3 x 630 uL). The resulting white suspension was stirred for 15 min, dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered washing with THF (100 mL) and ethyl acetate (100 mL). The filtrate was concentrated to provide **26** as a white solid (1.35 g, 100%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.83 (ddd, 4 H), 1.77 - 1.62 (m, 5 H), 1.57 (m, 1 H), 1.42 (m, 1 H), 1.30 - 0.96 (m, 5 H).



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## Step 3

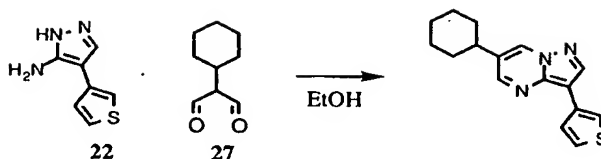
A solution of oxalyl chloride (2.39 g, 1.64 mL, 18.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at -60°C was treated with DMSO (2.94 g, 2.67 mL, 37.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) over 2 min. After 5 min, a solution of **26** (1.35 g, 8.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added and the resulting suspension was maintained at -60°C for 15 min. Triethylamine (8.6 g, 11.8 mL, 85 mmol) was then added and the reaction mixture was allowed to warm to 20°C. The quenched reaction was poured into water (200 mL) and washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by flash chromatography (40% Hexane/EtOAc) to provide **27** as a viscous oil [135 mg, 10%, *R<sub>f</sub>* = 0.34 (40% Hexane/EtOAc)]: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.26 (s, 2 H), 2.09 (tt, 1 H), 1.85 - 1.68 (m, 6 H), 1.39 - 1.13 (m, 5 H).



## Step 4

A solution of **27** (50 mg, 0.30 mmol) and **22** (47 mg, 0.30 mmol) in ethanol (5 mL) was heated at 75°C for 16 h. After cooling, the reaction mixture was concentrated, and the crude product was purified by flash chromatography (25% EtOAc/Hexane) to provide **6** as a yellow solid [54 mg, 63%, *R<sub>f</sub>* = 0.33 (25% EtOAc/Hexanes)]: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.48 (d, 1 H, *J* = 2.2 Hz), 8.44 (d, 1 H, *J* = 1.5 Hz), 8.30 (s, 1 H), 7.86 (dd, 1 H, *J* = 2.9, 1.1 Hz), 7.66 (dd, 1 H, *J* = 4.9, 1.2 Hz), 7.41 (dd, 1 H, *J* = 4.9, 2.9 Hz), 2.64 (m, 1 H), 2.03 - 1.80 (m, 5 H), 1.52 - 1.27 (m, 5 H); FAB MS (*M*<sup>+</sup>+1) calcd. for 284, found 284; Anal Calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>S (0.05 H<sub>2</sub>O): C, 67.59; H, 6.06; N, 14.78. Found C, 67.66; H, 6.12; N, 15.14.

- 25 -



Kinase inhibition is demonstrated in accordance with the following protocol.

5

### VEGF RECEPTOR KINASE ASSAY

VEGF receptor kinase activity is measured by incorporation of radio-labeled phosphate into polyglutamic acid, tyrosine, 4:1 (pEY) substrate. The phosphorylated pEY product is trapped onto a filter membrane and the incorporation of radio-labeled phosphate quantified by scintillation counting.

10

### MATERIALS

#### VEGF receptor kinase

The intracellular tyrosine kinase domains of human KDR (Terman, B.I. et al. Oncogene (1991) vol. 6, pp. 1677-1683.) and Flt-1 (Shibuya, M. et al. Oncogene (1990) vol. 5, pp. 519-524) were cloned as glutathione S-transferase (GST) gene fusion proteins. This was accomplished by cloning the cytoplasmic domain of the KDR kinase as an in frame fusion at the carboxy terminus of the GST gene. Soluble recombinant GST-kinase domain fusion proteins were expressed in *Spodoptera frugiperda* (Sf21) insect cells (Invitrogen) using a baculovirus expression vector (pAcG2T, Pharmingen).

20

25

#### Lysis buffer

50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM EDTA, 0.5% triton X-100, 10 % glycerol, 10 mg/ml of each leupeptin, pepstatin and aprotinin and 1mM phenylmethylsulfonyl fluoride (all Sigma).

30

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Wash buffer

50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM  
EDTA, 0.05% triton X-100, 10 % glycerol, 10 mg/ml of each  
leupeptin, pepstatin and aprotinin and 1mM phenylmethylsulfonyl  
fluoride.

Dialysis buffer

50 mM Tris pH 7.4, 0.5 M NaCl, 5 mM DTT, 1 mM  
EDTA, 0.05% triton X-100, 50 % glycerol, 10 mg/ml of each  
leupeptin, pepstatin and aprotinin and 1mM phenylmethylsulfonyl  
fluoride

10 X reaction buffer

200 mM Tris, pH 7.4, 1.0 M NaCl, 50 mM MnCl<sub>2</sub>, 10  
mM DTT and 5 mg/ml bovine serum albumin (Sigma).

Enzyme dilution buffer

50 mM Tris, pH 7.4, 0.1 M NaCl, 1 mM DTT, 10 %  
glycerol, 100 mg/ml BSA.

10 X Substrate

750 µg/ml poly (glutamic acid, tyrosine; 4:1) (Sigma).

Stop solution

30% trichloroacetic acid, 0.2 M sodium  
pyrophosphate (both Fisher).

Wash solution

15% trichloroacetic acid, 0.2 M sodium  
pyrophosphate.

Filter plates

Millipore #MAFC NOB, GF/C glass fiber 96 well  
plate.

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## METHOD

### A. Protein purification

1. Sf21 cells were infected with recombinant virus  
5 at a multiplicity of infection of 5 virus particles/ cell and grown at  
27 °C for 48 hours.
2. All steps were performed at 4°C. Infected cells  
were harvested by centrifugation at 1000 X g and lysed at 4 °C for  
30 minutes with 1/10 volume of lysis buffer followed by  
10 centrifugation at 100,000Xg for 1 hour. The supernatant was then  
passed over a glutathione Sepharose column (Pharmacia)  
equilibrated in lysis buffer and washed with 5 volumes of the same  
buffer followed by 5 volumes of wash buffer. Recombinant GST-  
KDR protein was eluted with wash buffer/10 mM reduced  
15 glutathione (Sigma) and dialyzed against dialysis buffer.

### B. VEGF receptor kinase assay

1. Add 5 µl of inhibitor or control to the assay in 50%  
DMSO.
- 20 2. Add 35 µl of reaction mix containing 5 µl of 10 X  
reaction buffer, 5 µl 25 mM ATP/10 µCi [<sup>33</sup>P]ATP (Amersham),  
and 5 µl 10 X substrate.
3. Start the reaction by the addition of 10 µl of KDR  
(25 nM) in enzyme dilution buffer.
- 25 4. Mix and incubate at room temperature for 15  
minutes.
5. Stop by the addition of 50 µl stop solution.
6. Incubate for 15 minutes at 4°C.
7. Transfer a 90 µl aliquot to filter plate.
- 30 8. Aspirate and wash 3 times with wash solution.
9. Add 30 µl of scintillation cocktail, seal plate and  
count in a Wallac Microbeta scintillation counter.

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### Human Umbilical Vein Endothelial Cell Mitogenesis Assay

Expression of VEGF receptors that mediate mitogenic responses to the growth factor is largely restricted to vascular endothelial cells. Human umbilical vein endothelial cells (HUVECs) in culture proliferate in response to VEGF treatment and can be used as an assay system to quantify the effects of KDR kinase inhibitors on VEGF stimulation. In the assay described, quiescent HUVEC monolayers are treated with vehicle or test compound 2 hours prior to addition of VEGF or basic fibroblast growth factor (bFGF). The mitogenic response to VEGF or bFGF is determined by measuring the incorporation of [<sup>3</sup>H]thymidine into cellular DNA.

### Materials

#### 15 HUVECs

HUVECs frozen as primary culture isolates are obtained from Clonetics Corp. Cells are maintained in Endothelial Growth Medium (EGM; Clonetics) and are used for mitogenic assays at passages 3-7.

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#### Culture Plates

NUNCLON 96-well polystyrene tissue culture plates (NUNC #167008).

#### 25 Assay Medium

Dulbecco's modification of Eagle's medium containing 1 g/ml glucose (low-glucose DMEM; Mediatech) plus 10% (v/v) fetal bovine serum (Clonetics).

#### 30 Test Compounds

Working stocks of test compounds are diluted serially in 100% dimethylsulfoxide (DMSO) to 400-fold greater than their desired final concentrations. Final dilutions to 1X concentration are

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made directly into Assay Medium immediately prior to addition to cells.

#### 10X Growth factors

- 5                    Solutions of human VEGF<sub>165</sub> (500 ng/ml; R&D Systems) and bFGF (10 ng/ml; R&D Systems) are prepared in Assay Medium.

#### 10X [<sup>3</sup>H]Thymidine

- 10                    [Methyl-<sup>3</sup>H]Thymidine (20 Ci/mmol; Dupont-NEN) is diluted to 80 uCi/ml in low-glucose DMEM.

#### Cell Wash Medium

- 15                    Hank's balanced salt solution (Mediatech) containing 1 mg/ml bovine serum albumin (Boehringer-Mannheim).

#### Cell Lysis Solution

1 N NaOH, 2% (w/v) Na<sub>2</sub>CO<sub>3</sub>.

#### 20    Method

1.                    HUVEC monolayers maintained in EGM are harvested by trypsinization and plated at a density of 4000 cells per 100 ul Assay Medium per well in 96-well plates. Cells are growth-  
25    arrested for 24 hours at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>.
2.                    Growth-arrest medium is replaced by 100 ul Assay Medium containing either vehicle (0.25% [v/v] DMSO) or the desired final concentration of test compound. All determinations  
30    are performed in triplicate. Cells are then incubated at 37°C/5% CO<sub>2</sub> for 2 hours to allow test compounds to enter cells.
3.                    After the 2-hour pretreatment period, cells are stimulated by addition of 10 ul/well of either Assay Medium, 10X



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VEGF solution or 10X bFGF solution. Cells are then incubated at 37°C/5% CO<sub>2</sub>.

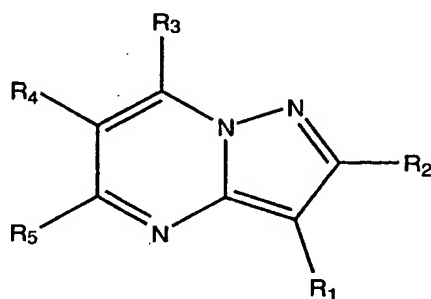
4. After 24 hours in the presence of growth factors, 10X [<sup>3</sup>H]Thymidine (10 ul/well) is added.
- 5 5. Three days after addition of [<sup>3</sup>H]thymidine, medium is removed by aspiration, and cells are washed twice with Cell Wash Medium (400 ul/well followed by 200 ul/well). The washed, adherent cells are then solubilized by addition of Cell Lysis Solution (100 ul/well) and warming to 37°C for 30 minutes. Cell lysates are  
10 transferred to 7-ml glass scintillation vials containing 150 ul of water. Scintillation cocktail (5 ml/vial) is added, and cell-associated radioactivity is determined by liquid scintillation spectroscopy.

Based upon the foregoing assays the compounds of formula I are inhibitors of VEGF and thus are useful for the  
15 inhibition of neoangiogenesis, such as in the treatment of ocular disease, e.g., diabetic retinopathy and in the treatment of cancers, e.g., solid tumors. The instant compounds inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC<sub>50</sub> values between 150-650 nM. These compounds also show  
20 selectivity over related tyrosine kinases (e.g. FGFR1 and the Src family).

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WHAT IS CLAIMED IS:

1. A compound in accordance with formula I:



I

or a pharmaceutically acceptable salt, hydrate or prodrug thereof,

wherein

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$R_1$  is H,  $C_{1-10}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{5-10}$  aryl, halo, OH,  $C_{3-10}$  heterocyclyl, or  $C_{5-10}$  heteroaryl; said alkyl, alkenyl,

alkynyl, aryl, heteroaryl and heterocyclyl being

optionally substituted with from one to three members selected

15

from  $R^a$ ;

$R_2$  &  $R_3$  are independently H,  $C_{1-6}$  alkyl,  $C_{5-10}$  aryl,  $C_{3-6}$  cycloalkyl, OH,  $NO_2$ ,  $-NH_2$ , or halogen;

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$R_4$  is H,  $C_{1-10}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{1-6}$  alkoxy  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{5-10}$  aryl,  $C_{3-10}$  heterocyclyl,  $C_{1-6}$  alkoxy  $NR_7R_8$ ,  $NO_2$ , OH,  $-NH_2$  or  $C_{5-10}$  heteroaryl, said alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three

25

members selected from  $R^a$ ;

$R_5$  is H, or  $C_{1-6}$  alkyl, OR, halo,  $NH_2$  or  $NO_2$ ;

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R<sup>a</sup> is H, C<sub>1-10</sub> alkyl, halogen, NO<sub>2</sub>, OR, -NR, NR<sub>7</sub>R<sub>8</sub>, R<sub>7</sub>R<sub>8</sub>, C<sub>5-10</sub> aryl, C<sub>5-10</sub> heteroaryl or C<sub>3-10</sub> heterocyclyl,

R is H, or C<sub>1-6</sub> alkyl; and

5 R<sub>7</sub>&R<sub>8</sub> are independently H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, COR, COOR, COO<sup>-</sup>, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, or C<sub>5-10</sub> heteroaryl or NR<sub>7</sub>R<sub>8</sub> can be taken together to form a heterocyclic 5-10 membered saturated or unsaturated  
10 ring containing, in addition to the nitrogen atom, one to two additional heteroatoms selected from the group consisting of N, O and S.

2. A compound in accordance with claim 1

15 wherein

R<sub>1</sub> is H, C<sub>1-10</sub> alkyl, C<sub>5-10</sub> aryl, C<sub>3-10</sub> heterocyclyl, or C<sub>5-10</sub> heteroaryl; said alkyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>;

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R<sub>2</sub>&R<sub>3</sub> are independently H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, OH, or halogen;

25 R<sub>4</sub> is H, C<sub>1-10</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>5-10</sub> aryl, C<sub>5-10</sub> heteroaryl, C<sub>3-10</sub> heterocyclyl, C<sub>1-6</sub> alkoxyNR<sub>7</sub>R<sub>8</sub>, NO<sub>2</sub>, OH, -NH<sub>2</sub> or C<sub>5-10</sub> heteroaryl, said alkyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from R<sup>a</sup>; and all other  
30 variables are as described above.

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3. A compound in accordance with claim 1 which

is:

- 3-(4-fluorophenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-chlorophenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
5 3-(3,4-methylenedioxyphenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-fluorophenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-chlorophenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
10 3-(3-thienyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-acetamidophenyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-thienyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
15 3-(3-acetamidophenyl)-6-(4-methoxyphenyl)pyrazolo(1,5-A)pyrimidine,  
3-(3-thienyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
20 3-(phenyl)-6-(4-chlorophenyl) pyrazolo(1,5-A)pyrimidine.  
3-(4-pyridyl)-6-(4-chlorophenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(4-methylphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(2-pyridyl) pyrazolo(1,5-A)pyrimidine,  
25 3-(4-pyridyl)-6-(2-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(2-pyrazinyl) pyrazolo(1,5-A)pyrimidine,  
3-(4-pyridyl)-6-(2-pyrazinyl) pyrazolo(1,5-A)pyrimidine,  
30 3-(3-pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-pyridyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine,  
3-(4 pyridyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-thienyl)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,

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3-(3-thienyl)-6-(4-hydroxyphenyl)pyrazolo(1,5-A)pyrimidine,  
3-(3-thienyl)-6-(4-(2-(4-morpholinyl)ethoxy)phenyl) pyrazolo(1,5-A)pyrimidine,  
3-(3-thienyl)-6-(cyclohexyl)pyrazolo (1,5-A)pyrimidine,  
5 3-(bromo)-6-(4-methoxyphenyl) pyrazolo(1,5-A)pyrimidine,  
3-(bromo)-6-(4-pyrimidyl) pyrazolo(1,5-A)pyrimidine,  
3-(phenyl)-6-(2-(3-carboxy)pyridyl) pyrazolo(1,5-A)pyrimidine,  
and  
3-(3-thienyl)-6-(4-pyridyl) pyrazolo(1,5-A)pyrimidine.

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4. A pharmaceutical composition which is comprised of a compound in accordance with claim 1 or a pharmaceutically acceptable salt, prodrug or hydrate thereof in combination with a carrier.

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5. A method of treating cancer in a mammalian patient in need of such treatment which is comprised of administering to said patient an anti-cancer effective amount of a compound of claim 1.

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6. A method of treating cancer in accordance with claim 5 wherein the cancer comprises cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

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7. A method in accordance with claim 5 wherein the cancer comprises histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, glioblastomas and breast carcinoma.

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8. A method of treating a disease in which neoangiogenesis is implicated, which is comprised of administering to a mammalian patient in need of such treatment a compound of formula I or a pharmaceutically acceptable salt, prodrug or hydrate

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thereof in an amount which is effective for reducing  
neoangiogenesis.

9. A method in accordance with claim 8 wherein  
5 the disease is an ocular disease.

10. A method of treating retinal vascularization  
which is comprised of administering to a mammalian patient in  
need of such treatment a compound of claim 1 or a  
10 pharmaceutically acceptable salt, prodrug or hydrate thereof in an  
amount which is effective for treating retinal vascularization.

11. A method of treating diabetic retinopathy which  
is comprised of administering to a mammalian patient in need of  
15 such treatment a compound of claim 1 or a pharmaceutically  
acceptable salt, prodrug or hydrate thereof in an amount which is  
effective for treating diabetic retinopathy.

12. A method of age-related macular degeneration  
20 which is comprised of administering to a mammalian patient in  
need of such treatment a compound of formula I or a  
pharmaceutically acceptable salt, prodrug or hydrate thereof in an  
amount which is effective for inflammation.

13. A method of treating inflammatory diseases  
25 which is comprised of administering to a mammalian patient in  
need of such treatment a compound of formula I or a  
pharmaceutically acceptable salt, prodrug or hydrate thereof in an  
amount which is effective for inflammation.

30 14. A method according to claim 13 treating  
wherein the inflammatory disease comprises rheumatoid arthritis,  
psoriasis, contact dermatitis and delayed hypersensitivity reactions.

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15. A method for inhibiting tyrosine kinase which comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a composition of claim 4.

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16. A method of preventing cancer in a mammalian patient in need of such treatment which is comprised of administering to said patient an anti-cancer effective amount of a compound of claim 1.

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17. A method of preventing cancer in accordance with claim 16 wherein the cancer comprises cancers of the brain, genitourinary tract, lymphatic system, stomach, larynx and lung.

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18. A method in accordance with claim 17 wherein the cancer comprises histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, glioblastomas and breast carcinoma.

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19. A method of preventing a disease in which neoangiogenesis is implicated, which is comprised of administering to a mammalian patient in need of such treatment a compound of formula I or a pharmaceutically acceptable salt, prodrug or hydrate thereof in an amount which is effective for reducing

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neoangiogenesis.

20. A method in accordance with claim 19 wherein the disease is an ocular disease.

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21. A method of preventing retinal vascularization which is comprised of administering to a mammalian patient in need of such treatment a compound of claim 1 or a pharmaceutically acceptable salt, prodrug or hydrate thereof in an amount which is effective for treating retinal vascularization.

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22. A method of preventing diabetic retinopathy which is comprised of administering to a mammalian patient in need of such treatment a compound of claim 1 or a  
5 pharmaceutically acceptable salt, prodrug or hydrate thereof in an amount which is effective for treating diabetic retinopathy.

23. A method of age-related macular degeneration which is comprised of administering to a mammalian patient in  
10 need of such treatment a compound of formula I or a pharmaceutically acceptable salt, prodrug or hydrate thereof in an amount which is effective for inflammation.

24. A method of preventing inflammatory diseases  
15 which is comprised of administering to a mammalian patient in need of such treatment a compound of formula I or a pharmaceutically acceptable salt, prodrug or hydrate thereof in an amount which is effective for inflammation.

20 25. A method according to claim 24 wherein the inflammatory disease comprises rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions.



## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/US98/10590

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : C01D 239/72, 401/00; A01N 43/54 US CL : 544/283, 284; 514/258, 259 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 544/283, 284; 514/258, 259 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched NONE Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Extra Sheet.		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN AN 1995:315545, KIYOKAWA et al. 'Condensed pyrazole derivatives, method of manufacturing the same, and androgen inhibitor'. Abstract to EP 594149 A2, 27 April 1994, see abstract.	1-7, 16-18
X — Y	Database HCAPLUS on STN AN 1993:603440 OKU et al. 'Preparation of condensed pyrazole derivatives with interleukin-1 and tumour necrosis factor inhibitory activity'. Abstract to EP 531901 A2, 17 March 1993,	1-4 ---- 1-4, 13, 14, 24 and 25
X	Database HCAPLUS on STN AN 1992:551008 ALLEN et al. 'imidazopyridazines and pyrazolopyrimidines [2-cyclopropyl-7-methyl-3-[2'-2'-(tetazolyl)biphenyl-4-yl]pyrazolo[1,5-a]pyrimidine-5-carboxylate], methods for their preparation and their use as angiotensin II antagonists, antihypertensives, anxiolytics and antidepressants'. Abstract to EP 490587 A1, 17 June 1992, see abstract.	1-4
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *A* document member of the same patent family	
Date of the actual completion of the international search 01 OCTOBER 1998		Date of mailing of the international search report 28 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer DWAYNE C. JONES Telephone No. (703) 308-1235

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/10590

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN AN 1996:181559, INOUE et al. 'Preparation of pyrazolo[1,5-a]pyrimidine derivatives as analgesics'. Abstract to JP 07309872 A2, 28 November 1995, see abstract.	1-4, 13, 14, 24 and 25
X	Database HCAPLUS on STN AN 1993:580816, INOUE et al. 'Preparation of pyrazolo[1,5-a]pyrimidine derivatives as pharmaceuticals'. Abstract to JP 05125079 A2, 21 May 1993, see abstract.	1-4, 13, 14, 24 and 25
X	Database HCAPLUS on STN AN 1993:213102, INOUE et al. 'Preparation of pyrazolo[1,5-a]pyrimidine derivatives antiinflammatory agents'. Abstract to WO 9218504 A1, 29 October 1992, see abstract.	1-4, 13, 14, 24 and 25
X	Database HCAPLUS on STN AN 1992:6580, INOUE et al. 'Preparation of pyrazolo[1,5-a]pyrimidine derivatives as drugs'. Abstract to JP 03204877 A2, 06 September 1991, see abstract.	1-4, 13, 14, 24 and 25

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/10590

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

REGISTRY, HCAPLUS structure search with the following terms: ?angiogenes/, (?neoplas? or ?tumor? or ?tumour?  
or ?malignan? or ?carcinom? or ?blastom?), (eye or retina or retinal), retino?, ?inflam?, (?rheumat? or ?arthritis? or  
?psorias?), (hypersensitiv? or sensitiv?), ?allerg?